

REMARKS

The August 28, 2003 Official Action and references cited therein have been carefully reviewed. In light of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of the application are respectfully requested.

At the outset, Applicant notes the revised restriction requirement set forth by the Examiner. Specifically, claim 8 has been rejoined with elected group IV. The Examiner also notes that claims 1, 23, 24, 33, 46, and 49 are linking claims and upon the allowance of a linking claim, the restriction requirement as to the linked invention shall be withdrawn and claims dependent from the linking claim shall be entitled to examination in this application.

At page 3 of the Official Action, the Examiner has further restricted group IV and groups I-III, V, VI, and XIII-XXXV to a species restriction of the sequence of the linking domain. Per a telephone interview, Applicant has elected the species of residues 205-219 of SEQ ID NO: 1. As required by the Examiner, Applicant hereby provides the following summary of the telephonic interview. Examiner Davis and Patrick Hagan engaged in a telephonic interview on or about August 21, 2003 wherein the species of residues 205-219 of SEQ ID NO: 1 was elected as the sequence of the linker domain, SEQ ID NO: 10 was elected as a general sequence for the linker domain, and the sequences on page 13 (i.e., SEQ ID NOs: 10-12) of the instant application were identified as linker domains. Applicant hereby reserves the right to file one or more continuation applications under 35 U.S.C. §120 on the subject matter ultimately withheld from consideration in the present application.

At page 7 of the Official Action, the Examiner has established the filing date (March 6, 2000) as the priority date of the instant application. Specifically, the Examiner

alleges that the applications to which priority is claimed fail to specifically recite the transcription factor EWS/ATF1.

Additionally, the Examiner has objected to the specification for allegedly citing references erroneously. The Examiner has also objected to claims 8 and 13 as allegedly unclear for the recitation of the term "involved."

At page 7 of the Official Action, the Examiner has rejected claims 1-4, 8-14, and 17-20 for allegedly failing to satisfy the written description requirement under 35 U.S.C §112, first paragraph. The Examiner contends the specification fails to provide support for the full breadth of the claims.

Claims 1-4, 8-14, and 17-20 are also rejected for allegedly failing to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. Specifically, the Examiner alleges that the specification does not provide enablement for modulating gene expression mediated by "any transcription factor" or "any fusion protein." The Examiner also contends the specification does not reasonably provide enablement for *in vivo* methods of modulation of gene expression.

The Examiner has also rejected claims 1-4, 8-14, and 17-20 under 35 U.S.C. §102(a) as allegedly anticipated by Bosilevac et al. (J. Biol. Chem., 1999, 274:34811-34818).

Claims 1-4, 8-14, and 17-20 are also rejected under 35 U.S.C. §103(a) as allegedly obvious over Orten et al. (J. Biol. Chem., 1994, 269:32254-33263) or Bosilevac et al. in view of Brown et al. (Oncogene, 1995, 10:1749-1756).

The foregoing objections and rejections constitute all of the grounds set forth in the August 28, 2003 Official Action for refusing the present application.

Applicant has cancelled claims 8 and 13 and avoided employing the allegedly unclear term "involved" in any of the newly added claims. Accordingly, the objection to claims 8 and 13 has been rendered moot.

The specification has also been amended to cite the proper references. An unintentional word-processing error occurred in the creation of this application wherein the reference list from one manuscript was inadvertently employed for the citations of another. Notably, all of the references added by amendment to the specification are present in the "List of References" of the application as originally filed, at page 103, line 12 through page 116, line 1. For example, as noted by the Examiner, the Hileman et al. reference at page 23, line 2 teaches novel fluorescent conjugates, but was cited after a disclosure that EWS/ATF1 is important for the initiation and maintenance of the neoplastic process. Applicant has replaced the Hileman et al. reference with the Ohno et al. reference which broadly discusses the role of EWS and EWS/ATF1 in tumors. Further support for this change and the changes made from page 22, line 11 through page 25, line 22 can be found in Bosilevac et al. (J. Biol. Chem. (1999) 274:34811-34818). Indeed, the specification within this citation is immediately recognizable as a near duplication of the discussion section in Bosilevac et al. (page 34816 right column through page 34818).

Applicant has also corrected additional incorrect citations. At page 26, line 5, the references of Busch et al. and Ellenberger et al. were deleted because while the text originally read "chromosomal translocation t(11; 22)", the word processor inserted reference numerals 11 and 22 (Busch et al. and Ellenberger et al., respectively) which do not speak to the chromosomal translocation. Additionally, at page 29, lines 16-17, the Hinrichs reference was deleted for not disclosing matter pertaining to PAX genes and replaced with the Strachan et al. reference (page 114, lines 17-18) which clearly discusses the roles of PAX (see title of reference).

Applicant has canceled claims 8-14 and added new claims 56-64. Support for new claim 56 can be found throughout the

instant specification including at page 5, line 11 through page 6, line 2. Claims 57-59 are supported, for example, by the disclosure at page 20, line 7 through page 21, line 11. Additionally, support for new claims 60 and 61 can be found throughout the instant specification including at page 11, lines 11-24. Lastly, new claim 62 is supported by the disclosure at page 12, line 8 through page 13, line 17 and support for claims 63 and 64 can be found at page 11, lines 11-24; page 20, lines 21-22; and Example 18, page 87, lines 15-20.

**CLAIMS 1-4, 8-14, AND 17-20, AS AMENDED, FULLY COMPLY WITH THE
WRITTEN DESCRIPTION REQUIREMENT SET FORTH IN 35 U.S.C. §112,
FIRST PARAGRAPH**

The Examiner has rejected claims 1-4, 8-14, and 17-20 for allegedly failing to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. The Examiner notes that the specification provides support for a method of inhibiting EWS/ATF1 transcription factor mediated gene expression by exposing the transcriptional factor to an antibody that binds a linker domain comprising amino acids 205-219 of SEQ ID NO: 1 which is adjacent to the DNA binding domain. However, the Examiner contends the specification fails to provide support for the full breadth of the claimed invention.

Specifically, it is the Examiner's position that the application has provided no example of the "disruption of transcriptional factors, other than ATF-1 and CREB" (page 10 of the Official Action). Applicant respectfully disagrees. The Examiner's attention is respectfully drawn to Examples 16-18 wherein the disruption of EWS/ATF1 binding to DNA and EWS/ATF1 mediated gene expression is described. See pages 83-90. Moreover, the instant application provides several methods for the identification of antibodies and antibody

fragments that can disrupt other transcription factors such as FL1 and EWS/FL1 as described in Examples 19 and 20 (pages 90-97) and PAX/FHXR as described in Examples 21 and 22 (pages 97-101).

At page 11 of the Official Action, the Examiner also claims that only a single antibody (sFv4) was provided in the specification that could disrupt the DNA binding ability of a transcription factor. Applicant again respectfully points out that in Example 3 (pages 49-51), mAb4 is described as inhibiting the DNA binding ability of ATF1. Moreover, Example 14 (pages 73-75) provides explicit instructions whereby a skilled artisan could generate sFv molecules with improved affinity or transcription inhibiting characteristics.

It is also the Examiner's position that the specification does not adequately describe the "genus of antibodies that could bind to and disrupt the binding of any transcriptional factor to DNA" because it is unknown whether the linking domains of other transcription factors are accessible to antibodies and whether such binding would prevent the binding of the transcription factor to DNA. Applicant submits the disclosure that mAb4 and sFv4 inhibit ATF1 and EWS/ATF1 binding to DNA is sufficient to meet the written description requirement for an antibody or antibody fragment binding to a linker domain within a transcription factor to inhibit transcription as set forth in claim 1. However, in an effort to advance prosecution of the instant application, Applicant has amended claim 1 to identify the transcription factor as the elected species of EWS/ATF1.

In light of the foregoing, Applicant submits that the rejection of claims 1-4, 8-14, and 17-20 for allegedly failing the written description requirement under 35 U.S.C. §112, first paragraph is improper and should be withdrawn.

CLAIMS 1-4, 8-14, AND 17-20, AS AMENDED, FULLY COMPLY WITH THE
ENABLEMENT REQUIREMENT SET FORTH IN 35 U.S.C. §112, FIRST
PARAGRAPH

The Examiner has rejected claims 1-4, 8-14, and 17-20 as allegedly failing to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. Specifically, the Examiner contends that the specification fails to enable methods for the modulation of gene expression mediated by any transcription factor. While enabling for an *in vitro* method of inhibiting EWS/ATF1 transcription factor mediated gene expression, it is the Examiner's position that the specification is not enabling for an *in vivo* method of inhibition.

The Examiner relies on the same arguments for both the enablement rejection and the written description rejection described above. Applicant contends, in light of the assays extensively described throughout the Examples section, that a skilled artisan would readily be able to ascertain if an antibody generated to a putative linker domain (such as those set forth in SEQ ID NOS: 10-12) of any transcription factor would be capable of modulating the expression of genes regulated by that transcription factor. Based on the amount of guidance provided, such experimentation can not be considered undue. However, as noted hereinabove, claim 1 has been amended to read on the elected species of the EWS/ATF1 transcription factor.

The Examiner also contends that the specification is not enabling for an *in vivo* method of gene expression modulation. Applicant strenuously disagrees with the Examiner. At the outset, Applicant disputes the Examiner's position that the art "does not recognize a reliable correlation between *in vitro* assay data and effective *in vivo*" immunotherapy. While Applicant agrees with the Examiner's contention that *in vitro* assays do not fully duplicate the complex conditions of the *in*

vivo environment, Applicant argues that a skilled artisan would recognize that *in vitro* results commonly have correlations and relevance to *in vivo* results.

Moreover, the Examiner raises the issues of delivery, stability, clearance, inactivation, and degradation of the agents *in vivo*. Applicant submits, however, that several monoclonal antibodies have been previously employed for the treatment of cancers. An example of such a monoclonal antibody is Rituxan® (Rituximab). Rituximab is a monoclonal antibody to CD20 which can be used to treat B-cell non-Hodgkin's lymphoma (see, in general, www.rituxan.com). Indeed, early studies with rituximab demonstrated the efficacy of the antibody against B-cell non-Hodgkin's lymphoma when provided intravenously (see abstract, McLaughlin et al., J. Clin. Oncol. (1998) 16:2825-33). Herceptin®, an antibody specific for Her2/Neu on breast tissue, has also proven efficacious for the treatment of breast cancer. Because rituximab and Herceptin®, both monoclonal antibodies, have been demonstrated to be efficacious in the treatment of cancers *in vivo*, Applicant submits that a skilled artisan would have an expectation of success for the use of other antibodies, such as the instantly claimed antibodies, in *in vivo* applications.

Additionally, Applicant submits that the scFv4 has been demonstrated to be efficacious *in vivo* in Jean et al. (Oncogene (2000) 19:2721-30). Specifically, intracellular expression of an sFv fragment derived from mAb4 (page 2722, left column) in human melanoma cells in an *in vivo* model was determined to render the cells apoptotic and inhibit tumor growth and metastasis (page 2725, right column). While the sFv fragment employed was directed to inhibiting ATF-1 transcriptional activity, a skilled artisan would readily appreciate that the sFv fragment would inhibit EWS/ATF1

mediated gene expression as taught in the instant application in Examples 16-18 (pages 83-90).

Inasmuch as expression of sFv fragments derived from mAb4 are efficacious in an *in vivo* milieu and antibodies, in general, can be delivered to humans for the effective treatment of cancer, Applicant submits that the disclosure enables the skilled artisan to treat tumors in a patient with the instantly claimed antibodies.

In light of the foregoing remarks, Applicant respectfully requests the withdrawal of the rejection of claims 1-4, 8-14, and 17-20 for allegedly failing to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph.

**CLAIMS 1-4, 8-14, AND 17-20 ARE NOT ANTICIPATED
BY BOSILEVAC ET AL.**

The Examiner has rejected claims 1-4, 8-14, and 17-20 under U.S.C. §102(a) as allegedly being anticipated by Bosilevac et al. The Examiner contends that Bosilevac et al. demonstrate the use of an antibody fragment, scFv4, to inhibit the binding of the EWS/ATF1 fusion protein with target DNA and teach the same method steps as the claimed invention. Notably, Bosilevac et al. was published December 3, 1999, less than one year prior to the priority date (March 6, 2000) of the instant application, as set forth by the Examiner.

Applicant contends that Bosilevac et al. fail to satisfy the requirement under §102(a) that a publication occur "before the invention thereof by the applicant for patent." Applicant respectfully point out to the Examiner that the instant inventor, Steven H. Hinrichs, is also a co-author of Bosilavac et al. It is logically self-evident that the publication relating to use of an antibody fragment to inhibit EWS/ATF1 binding to target DNA and related method steps in Bosilevac et al. could not have occurred before the invention thereof by Steven Hinrichs.

Furthermore, Bosilevac et al. is not citable as prior art in the present case, as the law is well settled that one's own work is not prior art under §102(a) even though it has been disclosed to the public in a manner or form which otherwise would fall under §102(a). In re Katz, 215 U.S.P.Q. 14 (CCPA 1982). Consequently, Bosilevac et al. also can not support a rejection under 35 U.S.C. §103. Ex Parte Oetiker, 23 U.S.P.Q.2d 1641 (BPAI 1992).

Therefore, Applicant respectfully submits the rejection of claims 1-4, 8-14, and 17-20 under 35 U.S.C. §102(a) is improper and requests its withdrawal.

**CLAIMS 1-4, 8-14, AND 17-20 ARE NOT OBVIOUS OVER ORTEN ET AL.
OR BOSILEVAC ET AL. IN VIEW OF BROWN ET AL.**

The Examiner has rejected claims 1-4, 8-14, and 17-20 under 35 U.S.C. §103(a) as allegedly being obvious over Orten et al. or Bosilevac et al. in view of Brown et al. Applicant notes that Bosilevac et al. is not prior art with respect to the subject matter of the claimed invention for the reasons set forth hereinabove. Thus, the Examiner's remaining rejection is that the claimed invention is allegedly obvious over Orten et al. in view of Brown et al. Applicant strenuously disagrees with the Examiner's position.

The Examiner claims Orten et al. teach a monoclonal antibody, mAb4, which binds to amino acids 205-219 of the transcription factor ATF1 and prevents the binding of ATF1 to DNA. The Examiner concedes that Orten et al. fail to teach 1) that the transcription factor is involved in a specific disease process, 2) that the antibody would be efficacious against EWS/ATF1, and 3) the use of a subcomponent of the antibody. The Examiner contends that Brown et al. teach the presence of the EWS/ATF1 transcription factor in malignant melanoma and that EWS/ATF1 is predicted to bind to DNA via the bZIP domain. The Examiner concludes that it would have been

prima facie obvious to a skilled artisan to replace the cells expressing ATF1 in the methods taught by Orten et al. with cells of Brown et al. expressing EWS/ATF1, and to modulate gene expression with the mAb4 antibody taught by Orten et al. In support of this position, the Examiner provides the following three reasons: 1) similar to ATF1, EWS/ATF1 could modulate gene expression via the ATF1 binding site of the target promoter; 2) EWS/ATF1 has been shown to be expressed in sarcomas; and 3) a skilled artisan would have expected the antibody, taught by Orten et al. to disrupt ATF1 binding to DNA, to also disrupt DNA binding activity of EWS/ATF1.

Applicant disagrees with the Examiner's position. Applicant submits that a skilled artisan would not have the reasonable expectation that an antibody, or fragment thereof, that binds to and inhibits the DNA binding properties of ATF1 would have the same effect on EWS/ATF1. Indeed, at page 15 of the instant Official Action (August 28, 2003), the Examiner indicates that "the structure of different transcription factors and their putative linker domains are however different and are not necessarily exposed such that an antibody fragment sFv could bind to" the linker domain. Moreover, the Examiner notes at page 16 of the Official Action that "the context of the protein [is] important and affect[s] the antibody binding affinity." Indeed, Bosilevac et al. teach that "the contribution of EWS to the overall conformation of the chimeric protein is unknown" and thus it is also unknown "whether the addition of the EWS domain would block the epitope of mAb4" (page 34814, left column). Inasmuch as the fusion protein EWS/ATF1 is twice the size of the ATF1 transcription factor (531 amino acids to 271 amino acids, see page 34813 of Bosilevac et al.), a skilled artisan would readily appreciate that the epitope of mAb4 could be obscured to antibody or antibody fragment entry and binding by the large EWS protein fused to ATF1.

Applicant has also provided an example of an obscured linker domain in the instant specification at page 18, lines 22 through page 19, line 16. Specifically, Applicant notes that the large mAb4, unlike the corresponding small sFv, is not capable of binding and inhibiting CREB because of the "complex structure" of CREB leading to "steric hinderance." Clearly, a skilled artisan would appreciate that the addition of about 260 amino acids (EWS) to a protein of 271 amino acids (ATF1) would likely dramatically alter the three dimensional structure of the protein and lead to changes in the accessibility of certain epitopes of the protein.

Based on the Examiner's own reasoning that linker domains of different transcription factors are not necessarily exposed to antibody binding and that the effects of the EWS fusion on the structure and availability of certain epitopes of ATF1 are completely unknown, a skilled artisan would be precluded from reasonably expecting mAb4 to be able to bind EWS/ATF1 and inhibit DNA binding in the same way mAB4 inhibits DNA binding by ATF1. Therefore, Applicant concludes that the rejection of claims 1-4, 8-14, and 17-20 under 35 U.S.C. §103(a) is untenable and should be withdrawn.


CONCLUSION

In view of the amendments presented herewith, and the foregoing remarks, it is respectfully urged that the objections and rejections set forth in the August 28, 2003 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number give below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By


Kathleen D. Rigaut, Ph.D., J.D.
PTO Registration No. 43,047

Telephone: (215) 563-4100

Facsimile: (215) 563-4044

Enclosures: Jean et al.

McLaughlin et al., abstract